UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,185	02/08/2002	Shih-Jen Liu	13886-002001 / 01P0325	3503

26161 7590 07/22/2005

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/072,185	LIU ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-27 and 36-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-27 and 36-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response received May 6, 2005 is acknowledged.

Claims 1-17 and 28-35 have been cancelled.

Claims 18, 21, 23, and 27 have been amended.

Claims 36-46 have been added.

Claims 18-27 and 36-46 are currently pending and are under examination in this office action as they read on the elected species of HSP70, PSA, and prostate cancer.

Specification

2. Applicant is thanked for correcting formatting errors present in the specification concerning the symbol for degrees Celsius.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 18, 21, 23, 24, and 27 stand rejected and new claims 36-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for the reasons of record in the office action mailed November 3, 2004.

Applicant's arguments filed May 6, 2005 have been fully considered but they are not persuasive. Specifically, Applicant has argued on pages 9 and 10 of the response that Applicant's amendment of claim 18 has limited it to those that contain a HSP-70 C-terminal fragment and that the genus of antigens is supported by the disclosure of the PSA antigen since " After all, as an antigen, by definition, induces an immune response, demonstrated induction of an immune response by a single antigen adequately represents operability of other antigens." Applicant is reminded that contrary to the quote obtained from page 10 of Applicants reply, an immunogen is any molecule that can elicit an adaptive immune response while an antigen is any molecule that reacts with antibodies (see the definitions of antigen and immunogen provided by Janeway et al., Immunobiology, Third Edition, pages G:2 and G:11). Note that the definition of antigen clearly indicates that not all antigens are immunogenic. As such, Applicant's logic that any antigen can be used in the instant claimed immunogenic composition is

flawed. Therefore, Applicant's specification does not provide support for the genus of all antigens based upon data obtained using PSA.

The currently recited limitation indicates that a DNA molecule flanked by specific nucleotide sequences encodes the human HSP-70 C-terminal fragment. These sequences appear to be subsequences of SEQ ID NO:3 and SEQ ID NO:4, although this is not indicated in the claims. None of the sequences of the HSP-70 or HSP-70 fusion constructs generated by Applicant are provided in the specification. Applicant's amendment to base claim 18 tries to define the meaning of the term "HSP-70 C-terminal fragment" by indicating sequences that flank the HSP-70 C-terminal fragment. However, using the techniques of molecular biology, any nucleotide sequence could be inserted between the two sequences currently recited in claim 18. This inserted sequence, whatever its source and sequence, would become, by Applicant's definition a C-terminal HSP-70 fragment, even if the inserted sequence otherwise shows no similarity to HSP-70. The specification does not appear to provide a representative number of sequences that are encompassed by this broad definition of HSP-70 C-terminal fragment, and as such the claimed invention does not have written support within the originally filed specification. Applicant is again directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 18-23 stand rejected and new claims 36-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Srivastava (U.S. Patent No. 5,985,270, see entire document) in view of Suzue et al. (Journal of Immunology, 1996, 156:873-879, see entire document) for the reasons of record presented in the office action mailed November 3, 2005.

Applicant's arguments filed May 6, 2005 have been fully considered but they are not persuasive. Specifically, Applicant argues on pages 10-12 of the response that first, neither of the above references teaches the claimed HSP-70 fragment and second, that

it is improper to combine the references since Suzue et al. use mycobacterial and not human HSP-70 protein. The examiner respectfully disagrees.

First, as has been indicated above in the rejection of paragraph 4 and as will be expanded in the new rejections necessitated by applicant's amendment presented in paragraphs 8, 9, and 11, the structure of the C-terminal HSP-70 fragment claimed by Applicant is not clear. As was indicated above, any sequence flanked by the recited nucleotide sequences would meet the claim limitation. Additionally, the claims recite that the C-terminal HSP-70 fragment is encoded by a DNA molecule, but it is not recited that the flanking polynucleotide sequences are translated and become part of the HSP-70 C-terminal polypeptide sequence. It is also noted that while the claims require that the polypeptide contain a C-terminal fragment of HSP-70, the inclusion of additional sequence from HSP-70 is not precluded. As such, additional HSP-70 sequence can be present in the teachings of the prior art and yet still anticipate the claimed invention. Srivastava does not disclose polynucleotide sequence data, but he does indicate the use of full length human HSP-70 which does contain a HSP-70 C-terminal fragment. As such, Srivastava teaches an HSP-70 molecule that contains the requisite HSP-70 sequence.

Second, Applicant has argued that one would not be motivated to covalently link antigens to human HSP-70 based on a teaching wherein mycobacterial HSP-70 is linked to an antigen because the two HSP molecules have different properties. As was indicated in the office action mailed November 11, 2004, a person of skill in the art would have been motivated to make HSP-70 fusion proteins because the can be easily

produced and purified in large amounts and can be more easily characterized because they contain identical numbers and positions of the fused antigen as taught by Suzue et al. None of these advantages is mycobacterial HSP-70 specific, and as such a person of ordinary skill in the art would have a reasonable expectation of success in enjoying these advantages when using human HSP-70 and the antigen PSA as was taught by Srivastava. Therefore, the rejection or record is maintained.

7. Claims 18 and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Srivastava (U.S. Patent No. 5,985,270, see entire document) in view of Suzue et al. (Journal of Immunology, 1996, 156:873-879, see entire document) as applied to claims 18-23 above, and further in view of Tong et al. (Cancer Research, 2001 61:7530-7535, see entire document) for the reasons of record set forth in the office action mailed November 3, 2004.

Applicant's arguments filed May 6, 2005 have been fully considered but they are not persuasive. Specifically applicant argues that the addition of Tong et al. does not remedy the deficiencies in the teachings of Srivastava and Suzue et al. The examiner respectfully disagrees for the reasons set forth supra. Therefore, the rejection of record is maintained.

The following are new rejections necessitated by Applicant's amendments to the claims received May 6, 2005.

8. Claims 18-27 and 36-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has amended base claim 18, the only independent claim currently pending, to include the term "stress protein." This term also appears in new dependent claims 36,41,and 43. The term "stress protein" is not defined in the specification, and the art recognized term "stress protein" encompasses more than heat shock proteins as evidenced by Attfield, US Patent No. 5,891,653, wherein it is taught that "stress proteins" include heat shock proteins, glucose regulated proteins, and Erp72 (see entire document, particularly lines 28-34 of column 1). Further, Applicant tries to define the term "stress protein" as encompassing heat shock proteins and heat shock fusion proteins in footnote 2 found on page 11 of the response. This definition is not part of the specification as filed and is also new matter. Therefore, Applicant's inclusion of the new term "stress protein" has broadened the scope of the claimed subject matter beyond what was disclosed in the specification, and this broadening constitutes new matter.

Applicant has also amended base claim 18 to include the new term "degenerate sequence thereof." In footnote 1 found on page 9 of the response filed May 6, 2005, Applicant provides a definition of what degenerate sequences are, and argues that their inclusion into the claim is not new matter. While any skilled artisan who reads the

claims would readily understand the term "degenerate sequences", this concept is not disclosed as being part of the invention in the specification as filed and therefore this limitation is also new matter.

Further amendments to base claim 18 indicate that the composition is free of human non-covalently bound antigens. Again, in the footnote on page 9 of the response Applicant argues that this is not new matter based on the example provided in the specification. It was known in the art that HSP-70 inherently associates with peptides, and that specific steps, such as purifying HSP-70 in the presence of excess ATP, must be performed to remove these peptides that inherently associate with HSP-70 (Srivastava, US Patent No. 5,837,251, see entire document particularly section 5.2.1, *Preparation and Purification of HSP-70-peptide complexes*, and section 5.2.4.1, *Peptides from stress protein-peptide complexes*). The specification does not appear to use such methods in generating the HSP-70 used in the examples disclosed by Applicant, and since the specification does not appear to expressly teach that the HSP-70 used in Applicant's experiments was free of noncovalently bound antigen, it is not clear that the HSP-70 used in Applicant's disclosed examples was in fact not complexed with non-covalently associated antigen. Since this limitation does not appear to be clearly taught by the specification, this limitation is also considered to be new matter.

9. Claims 18-27 and 36-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has amended the claim to indicate that the HSP-70 C-terminal fragment is encoded by a molecule flanked by two specified polynucleotide sequences. These sequences appear to be subsequences of SEQ ID NOs: 3 and 4, the primers used by Applicant to amplify the desired fragment of HSP-70 from human hepatocellular carcinoma HepG2 cDNA (see page 5, lines 6-24). Amplification of DNA is performed using the polymerase chain reaction (PCR), and results in a double stranded DNA product, with the sequence of the primer encoding SEQ ID NO:3 found on one strand and the sequence of SEQ ID NO:4 found on the other strand (see Alberts et al., Molecular Biology of the Cell, Third Edition, pages 308-331 for an overview of DNA cloning and engineering). The specification appears to indicate that SEQ ID NO:3 is located on the sense strand, i.e. the one that has a large open reading frame encoding HSP-70 protein. As such, SEQ ID NO:4, or a subsequence of it, is located on the DNA strand complementary to the one encoding HSP-70. As such, Applicant's examples teach a polynucleotide sequence encoding a fragment of HSP-70 flanked by the polynucleotide sequence of SEQ ID NO:3 and the complementary sequence of SEQ ID NO:4. The specification does not teach a polynucleotide encoding a fragment of HSP-70 flanked by subsequences of both SEQ ID NO:3 and SEQ ID NO:4. While it would be possible using standard molecular biology techniques to generate such a construct, the specification does not have an example of a polynucleotide encoding a fragment of HSP-70 flanked by subsequences of both SEQ ID NO:3 and SEQ ID NO:4, nor does it

provide guidance as to how this would be done or a teaching of why a skilled artisan would wish to generate such a construct. Neither the starting sequence of human HSP-70 used in the generation of C-terminal HSP-70 fragments nor the sequence of any of Applicant's HSP-70 or HSP-70 fusion proteins are disclosed.

Applicant has also indicated that the HSP-70 fragment or fusion protein of the claimed invention is free of non-covalently associated human antigens. It is known in the art that heat shock proteins, such as HSP-70, inherently bind peptides noncovalently and that specialized purification techniques are required to ensure that peptides are not noncovalently bound to the heat shock protein, as taught by Srivastava (US Patent No. 5,837,251, see entire document particularly section 5.2.1, *Preparation and Purification of HSP-70-peptide complexes*, and section 5.2.4.1, *Peptides from stress protein-peptide complexes*). The specification does not appear to indicate that such techniques were used in the examples of how to make the claimed products. As such it is not clear that the specification teaches how to make HSP-70 fragments or fusion proteins containing HSP-70 fragments that lack noncovalently bound antigens, human or otherwise.

Therefore, based upon the lack of guidance or working examples concerning how to generate a polynucleotide sequence encoding a C-terminal fragment of HSP-70 flanked by subsequences of both SEQ ID NO:3 and SEQ ID NO:4, the lack of sequence information concerning human HSP-70 and the HSP-70 C-terminal fragments and fusion proteins containing HSP-70 C-terminal fragments, and the lack of clear guidance or working examples demonstrating that the HSP-70 fragments taught by Applicant do

not contain noncovalently bound antigens, a person of skill in the art would be unable to make and use Applicant's claimed invention.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 18-27 and 36-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has claimed a composition wherein the HSP-70 C-terminal fragment is encoded by a polynucleotide flanked by two sequences. These sequences appear to be subsequences of the PCR primers used in the example provided by Applicant concerning the cloning of an HSP-70 C-terminal fragment. Since these subsequences are derived from primers, they will be found on opposite strands of the double stranded DNA molecule that is obtained via PCR. While the DNA obtained by PCR is double stranded, only one strand encodes a polypeptide sequence. As such, the strand of DNA encoding the HSP-70 fragment of the instant claims is flanked by one of the indicated sequences and by the complement of the other sequence. As such, the structure of the composition recited by Applicant in the instant claims is indefinite since it is not clear what Applicant is claiming by the recitation of a DNA sequence flanked by the recited sequences.

Claim Objections

12. Claims 18-27 and 36-46 are objected to because of the following informalities: Base claim 18 and dependent claim 40 recite specific polynucleotide sequences. These sequences are not identified by a SEQ ID number. As such the claims do not comply with the requirements of applications which contain sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825. Applicant is required to review the instant specification for compliance with the sequence rules set forth in 37 CFR 1.821-1.825.

13. The clarity of claim 18 would be improved if the word "wherein" was inserted between the word antigen and the on line 4 of claim 18. Applicant intends for the sequence limitations of HSP-70 to apply to both C-terminal HSP-70 fragments and fusion proteins containing C-terminal HSP-70 fragments (see the first full paragraph of page 11 of Applicant's response received May 6, 2005 for a statement verifying this interpretation). As currently written, without the word wherein, it is possible to interpret the limitations found in lines 5-7 as applying only to HSP-70 C-terminal fragments and not being applicable to HSP-70 fusion proteins.

Appropriate correction is required.

14. No claims are allowable.

15. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
July 18, 2005

Patrick J. Nolan, Ph.D.
Primary Examiner
Technology Center 1600